The authors reply

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We thank Dr. Bristrian for kindly appreciating our assessment of body composition changes during critical illness trough quantitative CT (qCT). This EPaNIC substudy, indeed, does not answer the clinical question when to start artificial feeding. This question has been addressed by 3 different high-quality RCT's including 6317 patients, unanimously showing no immediate vital or delayed functional benefit with parenteral nutrition initiated before day 7 (Early-PN) in the ICU (1-3). The largest RCT even demonstrated net harm by early-PN (1). Enhanced enteral nutrition during the first week in ICU, likewise, failed to provoke clinical benefit (4).

The aim of the EPaNIC qCT sub-study was to generate insight in the mechanisms of Early-PN's failure. Early-PN provoked a muscle composition shift towards water or fat and it increased the volume of intramuscular adipose tissue. Therefore, as suggested by Dr. Bristrian, lipogenesis is more likely the underlying mechanism than water retention. Secondly, Early-PN failed to prevent muscle wasting, both Early and Late-PN patients lost on average 7% of their initial muscle volume during the first week in ICU. Dr. Bristrian suggests that this failure is partly due to the small difference in protein intake between the two patient groups. As he rightly estimated, supplementation of insufficient enteral nutrition with commercial all-in-one PN preparations resulted, after one week, in on average 270 g of

additional protein administered to Early-PN patients. The cumulative protein intake did not correlate with muscle volume losses (r^2=0.004 and p=0.82). Furthermore, 63% of the administered nitrogen with Early-PN in EPaNIC was eliminated via the urine (5). In addition, as The_Nephro-Protective_Trial-authors recently reported at ESPEN 2013, increased protein intake up to the recommended 2 gram/kilogram/day provoked no clinical benefit and increased need for renal replacement therapy in the first adequately powered RCT studying different protein doses in critical illness. [https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12609001015235].

The hypothetical potential for improved tissue repair and immunological response with enhanced protein intake early in critical illness is refuted by clinical results. First, Early-PN provoked increased incidence and delayed recovery of ICU acquired muscle weakness, studied in 600 awake EPaNIC patients (6). Furthermore, microscopically, quadriceps muscle biopsy analysis indicated that the muscle weakness was not explained by muscle fiber size, but by suppressed autophagy. Autophagy, a catabolic cellular household mechanism crucial for clearing of cellular damage and mal-functioning organelles was clearly enhanced by Late-PN (6).

Secondly, none of the RCT's mentioned earlier (1-4) showed reduced incidence of new infections with enhanced feeding in the first week of critical illness. Even more, in EPaNIC, Early-PN provoked a dramatic increase in wound infections, air way infections and septiceamia (1). Whether this should be attributed to glucose rather than protein, lipids or total energy dose remains speculative. Nevertheless, administered macronutrient doses and obtained blood concentrations are more likely to be important than the osmolarity in the IV-bag prior to infusion.

In conclusion, the results of recent clinical, body composition and cell metabolism investigations all consistently question the paradigm of improving outcome in ICU through attenuation of early catabolism.

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